Potent spinal parenchymal AAV9-mediated gene delivery by subpial injection in adult rats and pigs.

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Public Summary:
Effective in vivo use of adeno-associated virus (AAV)-based vectors to achieve gene-specific silencing or upregulation in the central nervous system has been limited by the inability to provide more than limited deep parenchymal expression in adult animals using delivery routes with the most clinical relevance (intravenous or intrathecal). Here, we demonstrate that the spinal pia membrane represents the primary barrier limiting effective AAV9 penetration into the spinal parenchyma after intrathecal AAV9 delivery. We develop a novel subpial AAV9 delivery technique and AAV9-dextran formulation. We use these in adult rats and pigs to show (i) potent spinal parenchymal transgene expression in white and gray matter including neurons, glial and endothelial cells after single bolus subpial AAV9 delivery; (ii) delivery to almost all apparent descending motor axons throughout the length of the spinal cord after cervical or thoracic subpial AAV9 injection; (iii) potent retrograde transgene expression in brain motor centers (motor cortex and brain stem); and (iv) the relative safety of this approach by defining normal neurological function for up to 6 months after AAV9 delivery. Thus, subpial delivery of AAV9 enables gene-based therapies with a wide range of potential experimental and clinical utilizations in adult animals and human patients.

Scientific Abstract:
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